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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1635
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14

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|-----------------|------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/637,550 | ZHENG, CHAO-FENG |
| Examiner | Art Unit | |
| Jane Zara | 1635 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 22 February 2002.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 10-23, 25 and 26 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-9 and 24 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. | 6) <input type="checkbox"/> Other: _____ |

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File

DETAILED ACTION

This Office action is in response to the communication filed February 22, 2002, Paper No. 10.

Claims 1-26 are pending in the instant application.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Election/Restriction

Applicant's election of Group I in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 10-23, 25, 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 10.

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Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear from the description provided in claim 1 whether the conditionally active transactivation domain of CHOP is upstream and operably linked to the sequence specific DNA binding domain. Appropriate clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-9, 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a cell line comprising a stably integrated recombinant nucleic acid construct comprising a reporter gene operably linked to a recognition sequence for a sequence specific DNA binding protein and a stably integrated recombinant nucleic acid

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construct comprising a sequence encoding a fusion protein comprising a DNA binding domain which specifically binds to said recognition sequence. The specification and claims do not describe the elements that are essential to the function of the claimed invention comprising a recognition sequence for a sequence specific DNA binding protein and comprising a binding domain which specifically binds to the recognition sequence. The specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the genus comprising a recognition sequence for a sequence specific DNA binding protein and comprising a binding domain which specifically binds to the recognition sequence. The scope of the claims includes numerous structural variants and the genus is highly variant because a significant number of structural differences between members of a given genus is permitted. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. The specification fails to teach or adequately describe a representative number of species in the genus such that the common attributes or characteristics concisely identifying members of the proposed genus are exemplified, and, because each genus is highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed. Thus, Applicant was not in possession of the claimed genus.

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Claims 1-3, 5-9, 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cell line comprising a stably integrated recombinant nucleic acid construct comprising a reporter gene operably linked to a GAL4 recognition sequence and comprising a nucleic acid construct comprising a sequence encoding a fusion protein comprising a GAL4 binding domain, does not reasonably provide enablement for a cell line comprising a stably integrated recombinant nucleic acid construct comprising a reporter gene operably linked to any sequence specific DNA binding protein and a nucleic acid construct comprising a sequence encoding a fusion protein comprising any sequence specific DNA binding domain and a conditionally active transactivation domain of CHOP, whereby the DNA binding domain is (operably) linked upstream of the conditionally active transactivation domain of CHOP, and further whereby the activation of the transactivation domain of CHOP results in transactivation of the reporter gene due to fusion protein binding. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to cell lines comprising nucleic acid constructs comprising a reporter gene operably linked to any and/or all recognition sequences for any corresponding sequence specific DNA binding protein, and further comprising a stably integrated recombinant nucleic acid construct comprising sequences encoding a fusion protein comprising any sequence specific DNA binding protein which binds to the corresponding recognition sequence, and a conditionally active transactivation domain of CHOP, whereby activation of the CHOP domain

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leads to increased expression of the reporter gene as a result of the sequence specific DNA binding protein binding to the corresponding recognition sequence.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The nature of the invention. The claimed invention relies upon the a nucleic acid construct comprising a sequence encoding a fusion protein comprising a sequence specific DNA binding domain operably linked and downstream of the conditionally active transactivation domain of CHOP, whereby the transactivation of the CHOP domain leads to increased expression of the sequence specific DNA binding domain, which subsequently binds the corresponding recognition sequence that is operably linked and upstream of the reporter gene, thereby leading to increased reporter gene expression. The instant claims do not specify the orientation of the CHOP transactivation domain relative to the sequence specific DNA binding domain, however, and if the CHOP transactivation domain was located downstream of the sequence specific DNA binding domain, the activation of the CHOP domain would not lead to increased expression of the sequence specific DNA binding domain or the reporter gene.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification for the generation of stable cell lines comprising a stably integrated recombinant nucleic acid comprising a reporter gene operably linked to a recognition sequence for any and/or all sequence specific DNA binding proteins, nor for the transactivation of a reporter gene

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following binding of any and/or all sequence specific DNA binding proteins to their corresponding recognition sequences, nor for the transactivation or increased expression of a reporter gene following activation of the transactivation domain of CHOP which is located downstream of a sequence specific DNA binding protein.

The specification teaches the increased expression of a reporter gene operably linked and downstream of the GAL4 recognition sequence, following the activation of the transactivation domain of CHOP, operably linked and upstream of the GAL4 binding protein. One skilled in the art would not accept on its face the examples given in the specification of stable cell lines comprising nucleic acid constructs encoding a reporter gene operably linked and downstream of the GAL4 recognition sequence and further comprising stably integrated nucleic acid constructs encoding a fusion protein comprising the transactivation domain of CHOP upstream and operably linked to the GAL4 binding domain as being correlative or representative of cell lines comprising a stably integrated recombinant nucleic acid construct comprising a reporter gene operably linked to any sequence specific DNA binding protein and a nucleic acid construct comprising a sequence encoding a fusion protein comprising any corresponding sequence specific DNA binding domain and a conditionally active transactivation domain of CHOP, whereby the DNA binding domain is located upstream of the conditionally active transactivation domain of CHOP, and further whereby the activation of the transactivation domain of CHOP results in transactivation of the reporter gene due to fusion protein binding to the corresponding recognition sequence. The specification as filed fails to provide any particular guidance which

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resolves the known unpredictability in the art associated with the ability to construct recombinant nucleic acids comprising a reporter system which utilizes any and/or all sequence specific DNA binding domains and their corresponding recognition sequences, and further whereby the transactivation domain of CHOP is located downstream to the sequence specific DNA binding domain.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to cell lines comprising nucleic acid constructs comprising a reporter gene operably linked to any and/or all recognition sequences for any corresponding sequence specific DNA binding protein, and further comprising a stably integrated recombinant nucleic acid construct comprising sequences encoding a fusion protein comprising any sequence specific DNA binding protein which binds to the corresponding recognition sequence, and a conditionally active transactivation domain of CHOP, whereby activation of the CHOP domain leads to increased expression of the reporter gene as a result of the sequence specific DNA binding protein binding to the corresponding recognition sequence. In order to practice the invention over the scope claimed, it would require undue trial and error and undue experimentation beyond which is taught in the specification to practice the invention drawn to nucleic acid constructs comprising any and/or all sequence specific DNA binding domains and their corresponding recognition sequences. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of a representative number of species in the broad genus comprising nucleic acids encoding any

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and/or all sequence specific DNA binding domains and their corresponding recognition sequences and further whereby they are successfully utilized in the claimed reporter system for monitoring the activation of the transactivation domain of CHOP, as well as the de novo determination of the compatibility of such reporter systems in a particular host cell type, and further whereby said CHOP transactivation domain is located downstream of any and/or all sequence specific DNA binding domains. Since the specification fails to provide any particular guidance for broad genus claimed and since the ability to utilize any and/or all sequence specific DNA binding domains and their corresponding recognition sequences for measuring the activation of the transactivation domain of CHOP in a particular host cell is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1- 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al.

Wang et al teach stably transfected mammalian cells comprising a constitutively expressed fusion construct comprising the conditionally active transactivation domain of CHOP

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operably linked to a GAL4 DNA binding domain, and which stably transfected cells further comprise a reporter plasmid comprising the luciferase reporter gene operably linked to the GAL4 recognition sequence, whereby the transactivation of CHOP leads to the increased expression and binding of the sequence specific DNA binding domain (of GAL4) over basal or constitutive levels of expression in the mammalian host cell, and subsequently results in the transactivation and increased expression of the reporter gene over basal or constitutive levels of expression (See entire document, especially figure 3 and last two paragraphs of the text (pages 1348-1349).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-9 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al as applied to claims 1-7 above, and further in view of Lin et al and Wieder et al. Insofar as the claims are drawn to a mammalian cell line (or kit thereof) including HeLa cells comprising a stably integrated recombinant nucleic acid construct comprising a reporter gene such as luciferase operably linked to the GAL4 recognition sequence for a sequence specific DNA binding protein, and which cell line further comprises a stably integrated recombinant nucleic

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acid construct encoding a constitutively expressed fusion protein comprising a conditionally active transactivation domain of CHOP operably linked to the GAL4 DNA binding domain, wherein binding of said fusion protein to the GAL4 recognition sequence results in transactivation and increased expression of said reporter gene when said transactivation domain of CHOP, fused to the GAL4 DNA binding domain, is activated above basal levels of expression.

Wang et al is relied upon as cited in the above 102 rejection.

Wang et al does not teach the stable transfection of HeLa cells with the claimed nucleic acid constructs.

Lin et al teach the participation and interactions of various kinase cascades in cellular growth and differentiation, including the participation of stress activated protein kinases such as p38, which is a known activator of CHOP, in various cell lines including HeLa cells (See the abstract and first paragraph of the introduction on page 286; figures 4 and 6 on pages 288 and 289, respectively; and the last paragraph of the document on page 290).

Wieder et al teach the stable transfection of fibroblast derived cells including HeLa cells with various nucleic acid constructs (See col. 4, lines 11-16; col. 7, lines 20-32; col. 11).

It would have been obvious to one of ordinary skill in the art to stably transfet mammalian cells with a recombinant nucleic acid construct comprising a reporter gene operably linked to the GAL4 recognition sequence, and additionally with a nucleic acid construct encoding a fusion protein comprising the transactivation domain of CHOP operably linked to the GAL4

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binding domain because these constructs had been stably transfected into the fibroblast derived mouse cell line NIH3T3 cell line, as taught previously by Wang et al. One of ordinary skill in the art would have been motivated to study the regulation of CHOP in appropriate host cell lines (or using a kit comprising an appropriate host cell line) because CHOP has been implicated as being involved in kinase cascades which affect cellular events such as growth, differentiation and apoptosis, as taught previously by Wang et al and Lin et al. One of ordinary skill in the art would have been motivated to stably transfect these nucleic acid constructs (described above) into fibroblast derived cell lines such as NIH3T3 and HeLa cells in order to study the role of CHOP activation on cellular functions and activities because these fibroblast derived cell lines have been found to contain stress activated protein kinases, such as p38, known to activate the transcription factor CHOP, as taught previously by Wang et al and Lin et al, and one would have been motivated to study various forms of regulation of (the transactivation of) CHOP in appropriate stably transformed host cell lines known to participate in stress activation and other forms of regulation of kinase cascades involving CHOP. In addition, one of ordinary skill in the art would have been motivated to produce stable transfectants in these appropriate host cell lines rather than transient transfectants because stable transfectants provide a relatively permanent source of transfectants which express a reproducible amount of transfected nucleic acid constructs when the transfected cell line is grown under reproducible conditions, as opposed to transient transfectants, which cells are short-lived, and which must be generated anew with each experiment, and which provide variable levels of nucleic acid expression with every transfection.

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One of ordinary skill in the art would have expected that HeLa cells are appropriate host cells for stable transfections because stably transfecting HeLa cells is a routine technique known in the art as described by Wieder et al, who teach the stable transfection of HeLa cells using appropriate compatible nucleic acid constructs required for stable expression in the HeLa cell environment.

One of ordinary skill in the art would have been motivated to study the regulation of CHOP activation in HeLa cells because Lin et al teach the use of HeLa cells to study the interaction and participation of various kinase cascades in stress activation, including the participation and activation of p38, a known activator of CHOP. One of ordinary skill in the art therefore would have expected that the stably transfected HeLa cells provide an appropriate reagent to study the regulation of CHOP activation, including stress activation.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

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Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

July 15, 2002

*J Zara
TC 1600*